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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/784,513	02/23/2004	David H. Gorski	22311/04024	1509

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EXAMINER	
HUTSON, RICHARD G	
ART UNIT	**PAPER NUMBER**
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/784,513	GORSKI ET AL.	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *06 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-12* is/are pending in the application.

4a) Of the above claim(s) *11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-10 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/04;3/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment of claims 7 and 9-11, in the paper of 12/14/2006, is acknowledged. Claims 7-12 are at issue and are present for examination.

Election/Restrictions

Applicant's election without traverse of Group I, Claims 7-10 and 12, in the paper of 9/6/2006, is acknowledged.

Claim 11 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Applicants filing of information disclosure statements filed on 5/20/2004 and 3/24/2006, are acknowledged. Those references considered have been initialed.

Specification

The disclosure is objected to because of the following informalities:

The following portions of the specification list nucleic acid sequences which do not have associated with them a sequence identifier: page 17, lines 1-5. It is noted that applicant's amendment of the specification on 2/23/2004 appears to be related to similar material as is referenced above on page 17, lines 1-5, however this material is referenced at page 16, lines 5-14.

Applicants state that figure 1 is the nucleotide sequence of rat Gax gene with the predicted amino acid sequence and applicants also state that the rat Gax protein corresponds to SEQ ID NO: 2, however a comparison of the amino acid sequence of Figure 1 and that of SEQ ID NO: 2 reveals that these are in fact not the same sequences. For example both amino acid sequences are 303 amino acids in length, however the amino acid at position 189 of Figure 1 is a lysine, while the amino acid at position 189 of SEQ ID NO: 2 is an arginine. As applicants have chosen to limit all of the currently examined claims by SEQ ID NOs, it is critical that the information conveyed by the SEQ ID NOs is accurate. Applicants are directed to either correct this situation or appropriately explain.

Appropriate correction is required.

Claim Objections

Claims 7 and 10 are objected to because of the following informalities:

In claims 7 and 10, applicants recite "the amino acid sequence shown in Figure 3, SEQ ID NO: 4." It is suggested that this be amended to be clearer, such as "the amino acid sequence shown in Figure 3, **which is** SEQ ID NO: 4."

Claims 7 is drawn to nonelected subject matter (i.e. SEQ ID NO: 2).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is indefinite in that it is confusing in the recitation "...a polynucleotide comprising: (a) a fragment of clone 6 comprising nucleotides 699 to 941 of said polynucleotide; (b) a fragment of clone 23 comprising nucleotides 231 to 698 of said polynucleotide; (c) a fragment of clone 117 comprising nucleotides 119 to 230 of said polynucleotide and (d) a fragment of clone 131 comprising nucleotides 1 to 118 of said polynucleotide."

For the purpose of advancing prosecution claim 9 is interpreted as being drawn to any protein which inhibits vascular smooth muscle cell proliferation and is encoded by a polynucleotide comprising: (a) a fragment of clone 6 comprising nucleotides 699 to 941 of said polynucleotide; (b) a fragment of clone 23 comprising nucleotides 231 to 698 of said polynucleotide; (c) a fragment of clone 117 comprising nucleotides 119 to 230 of said polynucleotide and (d) a fragment of clone 131 comprising nucleotides 1 to 118 of said polynucleotide. Said fragments of clone 6, 23, 117 and 131 may be as little as a single codon triplet which encodes a single amino acid. Thus given this

interpretation the claim reads on essentially on any protein having the necessary functional limitation of inhibiting vascular smooth muscle cell proliferation.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 9 is directed to all possible proteins which inhibit vascular smooth muscle cell proliferation and are encoded by a polynucleotide comprising the following fragments: (a) a fragment of clone 6 comprising nucleotides 699 to 941 of said polynucleotide; (b) a fragment of clone 23 comprising nucleotides 231 to 698 of said polynucleotide; (c) a fragment of clone 117 comprising nucleotides 119 to 230 of said polynucleotide and (d) a fragment of clone 131 comprising nucleotides 1 to 118 of said polynucleotide (See above rejection under 112 second paragraph). It is noted that claim 9 is somewhat confusing in how it is written, however, for the purpose of advancing prosecution claim 9 is interpreted as being drawn to any protein which inhibits vascular smooth muscle cell proliferation and is encoded by a polynucleotide comprising: (a) a fragment of clone 6 comprising nucleotides 699 to 941 of said polynucleotide; (b) a fragment of clone 23 comprising nucleotides 231 to 698 of said

polynucleotide; (c) a fragment of clone 117 comprising nucleotides 119 to 230 of said polynucleotide and (d) a fragment of clone 131 comprising nucleotides 1 to 118 of said polynucleotide. Said fragments of clone 6, 23, 117 and 131 may be as little as a single codon triplet which encodes a single amino acid.

The specification, however, only provides a two representative species, one from rat and one from human encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship for the disclosed species (i.e. the inhibition of vascular smooth muscle cell proliferation). The specification also fails to describe additional representative species of these proteins by any identifying structural characteristics or properties other than the activity recited in claim 9 (i.e. the inhibition of vascular smooth muscle cell proliferation), for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim 9 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a protein which inhibits vascular smooth muscle cell proliferation, having the amino acid sequence of SEQ ID NO: 4, does not

reasonably provide enablement for any protein which inhibits vascular smooth muscle cell proliferation and is encoded by a polynucleotide comprising: (a) a fragment of clone 6 comprising nucleotides 699 to 941 of said polynucleotide; (b) a fragment of clone 23 comprising nucleotides 231 to 698 of said polynucleotide; (c) a fragment of clone 117 comprising nucleotides 119 to 230 of said polynucleotide and (d) a fragment of clone 131 comprising nucleotides 1 to 118 of said polynucleotide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claim 9 is so broad as to encompass any protein which inhibits vascular smooth muscle cell proliferation and is encoded by a polynucleotide comprising: (a) a fragment of clone 6 comprising nucleotides 699 to 941 of said polynucleotide; (b) a fragment of clone 23 comprising nucleotides 231 to 698 of said polynucleotide; (c) a fragment of clone 117 comprising nucleotides 119 to 230 of said polynucleotide and (d) a fragment of clone 131 comprising nucleotides 1 to 118 of said polynucleotide (See above 112 second paragraph rejection). The scope of the claims is not commensurate with the

enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to that protein having the amino acid sequence of SEQ ID NO: 4.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any protein which inhibits vascular smooth muscle cell proliferation and is encoded by a polynucleotide comprising: (a) a fragment of clone 6 comprising nucleotides 699 to 941 of said polynucleotide; (b) a fragment of clone 23 comprising nucleotides 231 to 698 of said polynucleotide; (c) a

fragment of clone 117 comprising nucleotides 119 to 230 of said polynucleotide and (d) a fragment of clone 131 comprising nucleotides 1 to 118 of said polynucleotide, because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting protein activity; (B) the general tolerance of such a protein to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the ability to inhibit vascular smooth muscle cell proliferation claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those proteins of the claimed genus having the claimed activity of inhibiting vascular smooth muscle cell proliferation.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any protein with any number of amino acid modifications having the claimed activity of inhibiting vascular smooth muscle cell

proliferation. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those proteins having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 9 is rejected under 35 U.S.C. 102(a) as being anticipated by Gorski et al. (Molecular and Cellular Biology (1993) 13:3722-3733, see IDS).

Gorski et al. teach the rat Gax cDNA sequence and the encoded protein from rat. This taught protein inhibits vascular smooth muscle cell proliferation and is encoded by a polynucleotide comprising the following fragments (a) a fragment of clone 6 comprising nucleotides 699 to 941 of said polynucleotide; (b) a fragment of clone 23 comprising nucleotides 231 to 698 of said polynucleotide; (c) a fragment of clone 117 comprising nucleotides 119 to 230 of said polynucleotide and (d) a fragment of clone 131 comprising nucleotides 1 to 118 of said polynucleotide.

Gorski et al., although authored by the inventors, also includes other non-inventors and therefore is considered "by others" and constitutes prior art. Filing of a declaration pursuant to In re Katz USPQ 14 (CCPA 1982) would be sufficient to overcome this rejection.

Claims 9 is rejected under 35 U.S.C. 102(a) as being anticipated by Candia et al. (Nucleic Acids Res. 21(21): 4982, October 1993, see IDS).

Candia et al. teach the amino acid sequence of Mox-2, a mammalian Gax protein having a molecular weight of approximately 30-36 kDa and comprising a homeodomain which comprises the amino acid sequence of amino acids 185 through 245 of SEQ ID NO: 4, comprises an OPA transcribed repeat and is at least 97% identical to SEQ ID NO: 4. This taught protein inhibits vascular smooth muscle cell proliferation and is encoded by a polynucleotide comprising the following fragments (a) a fragment of clone 6 comprising nucleotides 699 to 941 of said polynucleotide; (b) a fragment of clone 23 comprising nucleotides 231 to 698 of said polynucleotide; (c) a fragment of clone 117 comprising nucleotides 119 to 230 of said polynucleotide and (d) a fragment of clone 131 comprising nucleotides 1 to 118 of said polynucleotide. While Candia et al. does not disclose if this protein has the ability to inhibit smooth muscle cell proliferation, it meets the structural limitations of the claims and would therefore be expected to have the claimed property of inhibiting smooth muscle cell proliferation, absent clear and convincing evidence to the contrary. Thus claim 9 is anticipated by Candia et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 7-10 and 12 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,897,293. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of U.S. Patent No. 6,897,293, which is drawn to an isolated human protein comprising amino acid 1 through 302 of SEQ ID NO: 4 anticipates claims 7-10 drawn to an isolated protein which inhibits vascular smooth muscle cell growth and comprises the amino acid sequence of SEQ ID NO: 4. Further U.S. Patent No. 6,897,293 teach the expression of the above protein as part of a glutathione S-transferase fusion protein for ease in its purification and such would thus be obvious.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
2/26/2007